Therapeutic Targeting of the Hematopoietic Stem Cell Niche

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Adult hematopoietic stem cells (HSCs) are a powerful clinical tool, but some patients are refused transplantation because of inadequate stem cells in either their own or the allogeneic source of cells. Overcoming the problem of too few stem cells has been the basis for *ex vivo* expansion efforts for a decade without a clear method of success. Alternative options include improved donor yields in stem cell harvests or improved efficiency of engraftment of limited stem cell numbers. Rather than manipulating the stem cells directly, we focused on using a pharmacologic approach to target the microenvironment, or niche, where the hematopoietic stem cells reside to achieve therapeutic benefit. We and others previously showed that the osteoblast is a key component of the niche. Stimulating the osteoblast with parathyroid hormone (PTH) increased both the number of stem cells and the ability of irradiated mice to tolerate transplantation with limiting numbers of stem cells. The marked improvement in survival and marrow cellularity following transplantation raised concern that PTH plus the cytokine storm of transplantation could lead to premature exhaustion of the stem cell pool. To address this and other issues relevant for clinical application, we tested whether stem cell number or function was adversely affected by PTH treatment of the transplant recipient. Further, we asked whether PTH treatment of the donor mouse could increase the number of stem cells mobilized into the circulation per standard methods applied to patients and whether this could be accomplished after prior treatment with sequential cycles of cytotoxic chemotherapy. We demonstrated first that use of PTH in the transplant recipient did not deplete but rather increased the number of stem cells in the bone marrow and resulted in long-term engraftment. Second, PTH treatment of the donor mouse resulted in a significant increase in the HSC in the blood when mobilized by G-CSF. Third, stimulation of the niche with PTH during each cycle of chemotherapy protected or expanded the HSC population during multiple rounds of myelotoxic chemotherapy. Therefore, PTH may be a useful adjunct to bone marrow transplantation improving both the yield of stem cell donors and the engraftment potential in the recipient of even small numbers of stem cells. These effects can be accomplished by alteration of the stem cell niche rather than the stem cells themselves. Defining and understanding stem cell niches may offer new opportunities for stem cell based therapies.